

2. Studies of Cancer in Humans

2.1 T-Cell malignancies

2.1.1 HTLV-I-infection and adult T-cell leukaemia/lymphoma

Adult T-cell leukaemia/lymphoma (ATLL) was described as a distinct clinicopathological entity by Uchiyama *et al.* (1977). Seroepidemiological surveys on lymphoid neoplasms and healthy populations in the early 1980s demonstrated that HTLV-I and ATLL were both clustered in south-western Japan and in Caribbean islands (Hinuma *et al.*, 1982; Blattner *et al.*, 1983). In the mid-1980s and early 1990s, a number of other HTLV-I endemic areas with evidence of ATLL were recognized, chiefly in central and west Africa, South America and the Middle East, and the disease was also found among immigrants from these countries to Europe and the United States (Catovsky *et al.*, 1982; Hahn *et al.*, 1984; Williams *et al.*, 1984; Delaporte *et al.*, 1989b; Denic *et al.*, 1990; Meytes *et al.*, 1990; Sidi *et al.*, 1990; Cabrera *et al.*, 1994; Matutes & Catovsky, 1994; Pombo de Oliveira *et al.*, 1995).

(a) Clinical description

ATLL is a mature (post-thymic) T-cell malignancy which may be considered within the leukaemia/lymphoma syndromes. The disease arises in peripheral lymphoid tissues, e.g., nodes or skin, but a leukaemic picture is frequent.

(i) Distribution by subtype

ATLL has been classified into four subtypes: acute type, lymphoma type, chronic type and smouldering type, according to the clinicopathological features (Shimoyama *et al.*, 1991). The distinguishing features of the various forms of ATLL are summarized in Table 1. Among 1400 cases of ATLL registered throughout Japan during 1990–1993, 914 cases (65%) were classified as the acute type (prototype of ATLL), 330 cases (24%) as the lymphoma type, 83 cases (6%) as the chronic type and 73 cases (5%) as the smouldering type (see Table 1) (T- and B-Cell Malignancy Study Group, 1996).

Table 1. Average age, sex ratio and clinical findings in patients with adult T-cell leukaemia/lymphoma by subtype in Japan (1990–93)

Subtype	No. of cases (%)	Age (\pm SE)	Sex ratio (male : female)	Skin lesion (%) ^a	Hypercalcaemia (%) ^{a,b}
Acute	914 (65.3)	58.2 \pm 0.39	1.2	31.4 %	32.8
Lymphoma	330 (23.6)	59.4 \pm 0.66	1.2	14.0%	15.4
Chronic	83 (5.9)	58.8 \pm 1.41	0.9	31.8%	1.1 ^c
Smouldering	73 (5.2)	58.5 \pm 1.59	1.0	55.7%	0
Total	1400 (100)	58.6 \pm 0.32	1.2	28.5%	25.0

From T- and B-Cell Malignancy Study Group (1996); SE, standard error

^a Calculated by the Working Group

^b Adjusted Ca⁺⁺ value \geq 5.5 mEq/L

^c One case of chronic-type ATLL showed 5.8 mEq/L (unadjusted value, 5.4 mEq/L)

As the clinical spectrum of conditions now accepted as part of ATLL has extended, these conditions have become increasingly difficult to distinguish from other types of T-cell malignancy and sometimes diagnoses have depended on the identification of HTLV-I antibody or genomic material in the subjects, making the understanding of the relationship between this virus and these manifestations difficult to disentangle.

Ocular manifestations, particularly retinitis, resulting from intraocular infiltration by leukaemic cells, can precede or occur during the course of ATLL (Kohno *et al.*, 1993; Kumar *et al.*, 1994).

Acute adult T-cell leukaemia/lymphoma

This is the most frequent presentation of ATLL, corresponding to two thirds of the cases. The main clinical manifestations are organomegaly, high white blood cell count with lymphocytosis and often skin involvement. Lactate dehydrogenase levels are elevated and hypercalcaemia is frequent, although these two parameters are not essential diagnostic criteria of this clinical form. Other less frequent manifestations include CNS involvement, pleural effusions or ascites, lung infiltrates due either to opportunistic infections or to leukaemic infiltration of the lungs and, more rarely, primary involvement of the gastrointestinal tract (Hattori *et al.*, 1991; Nishimura *et al.*, 1994), the Waldeyer's ring (Ohguro *et al.*, 1993) or the cardiac valves (Gabarre *et al.*, 1993).

Lymphomatous adult T-cell leukaemia/lymphoma

This corresponds to the tissue-based ATLL with no evidence of peripheral blood involvement and no lymphocytosis at onset. Many cases develop to leukaemic status at terminal stage. Otherwise, the symptoms are identical to those of the acute (or prototype) form of ATLL, although hypercalcaemia is less common.

Chronic adult T-cell leukaemia/lymphoma

This form is characterized by persistent T-cell lymphocytosis ($> 4 \times 10^9/L$) with atypical cells, minor or no lymphoid organ or skin involvement and lack of systemic symptoms. The lactate dehydrogenase level may be elevated. In both smouldering and chronic ATLL, serum calcium levels are within the normal range.

Smouldering adult T-cell leukaemia/lymphoma

Smouldering ATLL, sometimes referred to as pre-ATLL or pre-leukaemic ATLL (Kinoshita *et al.*, 1985b), is characterized by skin lesions (which usually respond to topical corticosteroids), frequently lung infiltrates and an absence of systemic symptoms (Yamaguchi *et al.*, 1983; Takatsuki *et al.*, 1985; Shimoyama *et al.*, 1991). Patients may be asymptomatic, the disease being discovered during incidental examination. The white blood cell count is normal except for the presence of a few ($< 4\%$) circulating abnormal lymphocytes. Abnormal lymphocytes are sometimes seen in healthy carriers of HTLV-I (Matutes *et al.*, 1986), but in smouldering ATLL, there is clonal integration of viral DNA, as demonstrated by Southern blot.

Smouldering ATLL can be considered to be an early stage of the acute and lymphoma types of ATLL. There does not seem to be a natural progression from the smouldering stage to acute ATLL within a period of months to years (Yamaguchi *et al.*, 1983; Cabrera *et al.*, 1994; Matutes & Catovsky, 1994; Pombo di Oliveira *et al.*, 1995).

Pre-leukaemic cases of ATLL with monoclonal proliferation of abnormal lymphocytes (see 'Histological characteristics' below) without clinical signs or symptoms were studied in south-western Japan (Ikeda *et al.*, 1990). The prevalence rate of pre-leukaemic ATLL among HTLV-I carriers over 30 years of age was estimated as 2% and the age distribution of pre-leukaemic cases, ranging from 30 to 77 years, was no different from that of overt cases of ATLL. The pre-leukaemic stage is presumed to be the clinical stage which precedes ATLL, but it remains possible that an HTLV-I carrier may develop symptoms of ATLL directly, without going through the pre-leukaemic stage. [The Working Group noted that the distinction between pre-ATLL and smouldering ATLL is not well defined.]

(ii) *Laboratory findings (Table 2)*

Hypercalcaemia is the most distinctive abnormality related to ATLL because it is extremely rare in other lymphoid neoplasms (Grossman *et al.*, 1981; Matutes & Catovsky, 1992; Yamaguchi, 1994). It is more frequent in the acute form with high white blood cell count and is rarely associated with osteolytic lesions. Hypercalcaemia is related to the release of cytokines (chiefly a parathyroid-hormone-related protein (PTH-rP), IL-1 and TNF- β) by the malignant cells, with serum levels of parathyroid hormone and vitamin D₃ remaining within the normal range. This cytokine-mediated mechanism is supported by the findings that the gene encoding PTH-rP is continuously transcribed in ATLL cells (Watanabe *et al.*, 1990), that the cells express a high level of PTH-rP mRNA and that, when cultured, they release PTH-rP into the medium (Honda *et al.*, 1988). Other biochemical abnormalities that are also found in other T-cell

malignancies are high levels of lactate dehydrogenase and β_2 -microglobulin; the latter is released either by the tumour cells or secondary to cytokine secretion by non-malignant cells. Both parameters are related to a poor outcome and survival (Shimamoto *et al.*, 1990a; Tsuda *et al.*, 1992).

Table 2. Diagnostic criteria of clinical subtypes of adult T-cell leukaemia/lymphoma

Feature	Smouldering	Chronic	Lymphoma	Acute
Lymphocytosis ^a	$< 4 \times 10^9/L$	$> 4 \times 10^9/L$	$< 4 \times 10^9/L$	$> 4 \times 10^9/L$
Lactate dehydrogenase	Normal or < 1.5 the normal limit	< 2 the normal limit	Variable ^b	Variable ^b
Calcium	Normal	Normal	Variable ^b	Variable ^b
Skin	Involved	Variable ^b	Variable ^b	Variable ^b
Lung	Often involved	Variable ^b	Variable ^b	Variable ^b
Systemic involvement ^c	No	No or minor	Variable ^b	Variable ^b

Adapted from Shimoyama *et al.* (1991) and Cann & Chen (1996)

^a With $> 5\%$ atypical 'flower' cells except in the lymphoma form

^b Not considered for the classification of the ATLL subtype

^c Enlargement of lymph nodes, spleen, liver, central nervous system, gastrointestinal tract or other organ involvement

(iii) Histological characteristics

The diagnosis of ATLL is based on clinicopathological features and a number of laboratory parameters, including peripheral blood cell morphology, histopathology, immunological markers and demonstration of the presence of HTLV-I by serology or molecular analysis. The blood picture in the leukaemic forms of ATLL is pleomorphic, the predominant cell being a medium-sized lymphocyte with a highly irregular, frequently polylobated nucleus, that is often called a 'flower' cell. Circulating immunoblasts may be present in small numbers but they usually predominate in the lymphoid tissues. This blood picture is usually, but not always, distinguishable from that seen in Sézary syndrome, in which the cells have a hyperchromatic cerebriform nucleus (Matutes & Catovsky, 1992). The bone marrow is usually not heavily involved but trephine biopsy may show proliferation of osteoclasts and bone reabsorption, features which relate to the hypercalcaemia.

Histological analysis is essential in the lymphoma form of ATLL. However, there is no unique histological pattern of lymphoid involvement in ATLL, which may be very similar to that of other peripheral T-cell lymphomas. The lymph nodes show effacement of the normal architecture by lymphoid cells of different size, varying from small to large (mixed-cell pattern) (Lennert *et al.*, 1985). Cases with unusual histology or even with a clinical picture resembling that of Hodgkin's disease have been described (Duggan *et al.*, 1988; Ohshima *et al.*, 1991a; Picard *et al.*, 1990). The histological pattern of skin infiltration is not specific either; dermal infiltration by pleomorphic cells is often observed, but in some cases epidermotropism and Pautrier's microabscesses are seen.

These may also occur in Sézary syndrome and mycosis fungoides (Matutes & Catovsky, 1992; Whittaker *et al.*, 1993; Arai *et al.*, 1994; Pombo de Oliveira *et al.*, 1995). Therefore, differentiating between Sézary syndrome or other T-cell lymphomas and ATLL can be difficult on the basis of histological results.

Immunological markers reveal that ATLL cells have a mature post-thymic T-cell phenotype. The most common phenotype of ATLL cells is CD4⁺, CD8⁻, but a few patients may have unusual phenotypes such as CD4 loss, CD8 expression or both. In the rare cases with CD4⁺, CD8⁺ T-cells, the disease appears to have a more aggressive course (Tamura *et al.*, 1985). The thymic markers TdT and CD1a are always absent. Tumour cells are often positive for CD2 and CD5 markers but usually negative for CD7 (Matutes & Catovsky, 1992). CD3 may be absent or only weakly expressed on the membrane (Tsuda & Takatsuki, 1984) but is, as a rule, expressed in the cytoplasm (Matutes & Catovsky, 1992). A characteristic, but not specific, feature of ATLL cells is the strong expression of the p55 α -chain of the IL-2 receptor, detected by the monoclonal antibody CD25 (Uchiyama *et al.*, 1985; Yodoi & Uchiyama, 1986; Matutes & Catovsky, 1992; Yamaguchi, 1994); other T-cell activation antigens, such as HLA-DR determinants and CD38, may also be expressed. In addition, soluble IL-2 receptors can be detected in the serum of these patients and the levels seem to relate to tumour burden (Yamaguchi *et al.*, 1989). It has been shown that the high numbers of IL-2 receptors in the membrane of ATLL cells result from the continuous transcription of the IL-2 receptor gene (Yodoi & Uchiyama, 1986). These observations suggest that IL-2 receptors play a key role in the etiopathogenesis or progression of the disease.

In spite of the CD4⁺, CD8⁻ phenotype, ATLL cells are not helper cells functionally but act as potent suppressors of B-cell differentiation (Yamada, 1983; Miedema *et al.*, 1984). It is uncertain whether this function is direct or is mediated by an indirect mechanism through a suppressor CD8⁺ T-cell subset. One consequence may be that some patients have concomitant disease related to immune suppression.

(iv) Genetic studies

In ATLL, a range of chromosomal abnormalities occur but, unlike those seen in some lymphoid malignancies, such as Burkitt's lymphoma, they are not specific. Abnormalities may involve chromosomes 3, 7 and X, and/or affect 6q, 14q, 3q, 1q and 10p (Shimoyama *et al.*, 1987; Kamada *et al.*, 1990). They are often more complex and are more frequently found in the acute and lymphomatous forms than in smouldering or chronic ATLL, which suggests that they correlate with disease progression.

Familial ATLL has been documented in HTLV-I endemic regions (Kawano *et al.*, 1984; Miyamoto *et al.*, 1985; Matutes & Catovsky, 1994) and less frequently in countries with low HTLV-I seroprevalence such as the United Kingdom (Matutes *et al.*, 1995a). In some families, several cases of TSP/HAM and ATLL have been seen (Uozumi *et al.*, 1991; Plumelle *et al.*, 1993) and the coexistence of the two diseases in the same patient has been described (Cartier *et al.*, 1995; Harrington *et al.*, 1995). The fact that, in the familial clusters, patients did not always share the same household suggests that it was the genetic background rather than the environment which influenced the development of ATLL. Early exposure to HTLV-I, e.g., neonatal or during childhood, seems to be

important for the development of ATLL, as the disease occurs many years after the retroviral infection, in contrast to TSP/HAM, which may develop shortly after infection by HTLV-I.

(v) *Prognosis*

ATLL is an aggressive malignancy with poor prognosis and short median survival ranging from 5 to 13 months in all areas (Shimamoto *et al.*, 1990a,b; Lymphoma Study Group (1984–1987), 1991; Shih *et al.*, 1991; Plumelle *et al.*, 1993; Matutes & Catovsky, 1994; Yamaguchi, 1994). Patients respond poorly to chemotherapeutic schedules used successfully against other high-grade lymphomas (Shimamoto *et al.*, 1990b; Matutes & Catovsky, 1994; Mercieca *et al.*, 1994). Experimental approaches such as therapy with antibody against the IL-2 receptor anti-Tac have yielded only transient responses (Waldmann *et al.*, 1988, 1995). There have, however, been reports of good response to a combination of α -interferon and zidovudine (Gallo, 1995; Gill *et al.*, 1995; Hermine *et al.*, 1995). The mechanism of action of this therapy is unknown. Furthermore, the duration of the response remains to be evaluated.

Patients with the smouldering and chronic forms of ATLL usually have a stable or very slowly progressive course and, during this phase, clinical problems are easier to control than in the acute forms. Generally, such patients are not treated aggressively.

(vi) *Prevention of ATLL*

Prevention of ATLL and/or cancers associated with HTLV-I is difficult, as the secondary factors promoting the evolution from healthy carrier status to ATLL or neoplasia are unknown. Although spontaneous remission of ATLL has been reported (Shimamoto *et al.*, 1993), this appears to be extremely rare. Experimental work has shown that inhibitors of thioredoxin reductase, such as retinoic acid derivatives, are able to inhibit DNA synthesis and growth and replication of HTLV-I-infected cells and therefore have a potential role in the treatment of HTLV-I carriers (U-Taniguchi *et al.*, 1995).

(b) *Epidemiology*

Consideration of the epidemiological evidence concerning the relationship between HTLV-I and ATLL must be viewed in the light of the history of HTLV-I's discovery in ATLL-endemic parts of the world. Reports in the early 1980s from these regions (discussed above) found a very high prevalence (> 90%) of HTLV infection in ATLL patients, compared with much lower population prevalence in the area from which the cases came. A few patients with clinical features indistinguishable from those of ATLL have, however, been reported in whom HTLV-I infection cannot be demonstrated (Shimoyama *et al.*, 1986, 1987; Pombo de Oliveira *et al.*, 1995).

The concordance between HTLV-I positivity and ATLL was so high in the endemic areas that HTLV-I became widely accepted as the cause of ATLL, and the presence of HTLV-I infection was adopted as an additional diagnostic criterion for ATLL for lesions in which the clinical findings were ambiguous. This practice complicates assessment of the association between HTLV-I and ATLL.

When the clinical and laboratory features characteristic of ATLL are present, serological assays for HTLV-I antibodies almost always show a strongly reactive test. However, if the features are atypical, DNA analysis by Southern blot using probes specific to HTLV-I sequences may be needed to demonstrate the clonal integration of HTLV-I in the tumour cells. All cases of ATLL have proviral HTLV-I DNA integrated in a monoclonal fashion, according to Yoshida *et al.* (1984). Therefore, the absence of HTLV-I clonal integration may be construed as evidence against this diagnosis in a case. In addition, DNA analysis helps to distinguish cases of smouldering ATLL from healthy carriers.

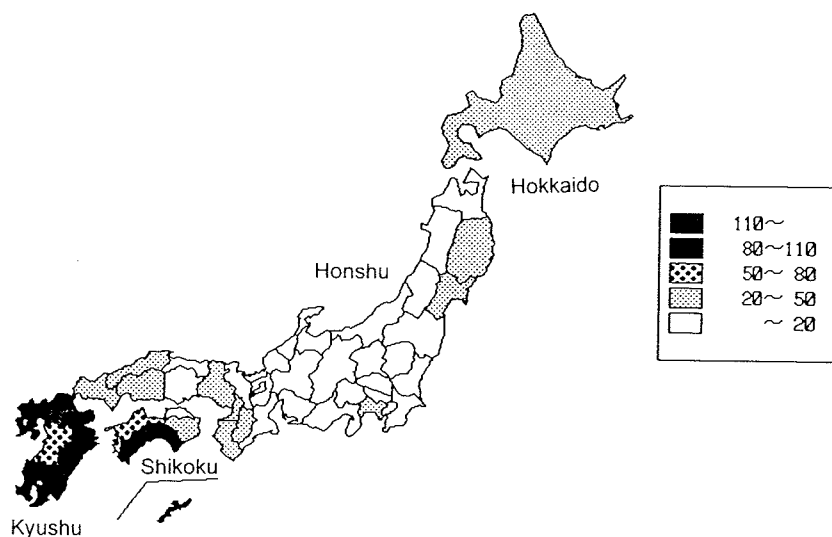
(i) *Geographical distribution*

Following the first report of ATLL cases from Japan by Uchiyama *et al.* (1977), 10 familial cases of ATLL were reported in the south-western part of Japan (Ichimaru *et al.*, 1979), where ATLL is highly endemic. A nationwide study, implemented in Japan soon after the original description, revealed that 50% of ATLL patients were registered in the southern Japanese island of Kyushu (see Figure 7). Only 25% were from major cities (Takatsuki *et al.*, 1977; Uchiyama *et al.*, 1977; Tajima *et al.*, 1990b; T- and B-cell Malignancy Study Group, 1988; Tajima, 1990; Tajima *et al.*, 1994), and 80% of these cases had been born in Kyushu. The sex ratio (male/female) is around 1.2 in Japan (T and B-cell Malignancy Study Group, 1996).

T-Cell leukaemia/lymphomas are not reported routinely as a separate diagnostic group in cancer incidence and mortality statistics. Their geographical distribution can, thus, be derived only from specific reports (or surveys) and the picture obtained is heavily influenced by the extent to which disease surveillance has been carried out in various areas. Studies in Brazil (Pombo de Oliveira *et al.*, 1990; Matutes *et al.*, 1994; Pombo de Oliveira *et al.*, 1995), in Gabon (Delaporte *et al.*, 1993) and in French Guiana (Gérard *et al.*, 1995) have demonstrated that the incidence of ATLL will continue to be greatly underestimated unless a specific search is carried out. This is mainly due to the acuteness and rapid evolution of the disease, so that many patients die before diagnosis can be made, as well as to confusion of ATLL with pathologically similar diseases, such as Sézary syndrome, mycosis fungoides and other types of T-cell non-Hodgkin's lymphoma (Gessain *et al.*, 1992b; Matutes & Catovsky, 1994; Pombo de Oliveira *et al.*, 1995). Furthermore, serological confirmatory tests for HTLV-I, such as western blot and/or molecular analyses, are not readily available in most countries. However, the geographical distribution of ATLL appears to be similar to that of HTLV-I, with rough correspondence of the relative prevalences of the conditions in different areas (see Section 1.3). ATLL has a high incidence in the south-western regions of the Japanese archipelago (Hinuma *et al.*, 1982; Clark *et al.*, 1985b; T- and B-cell Malignancy Study Group, 1985; Tajima & Cartier, 1995; T- and B-cell Malignancy Study Group, 1996). It is also prevalent in most other HTLV-I-endemic areas, including intertropical Africa, South and Central America and Iran (Clark *et al.*, 1988; Pombo de Oliveira *et al.*, 1990; Rio *et al.*, 1990; Gessain *et al.*, 1992a; Blank *et al.*, 1993; Delaporte *et al.*, 1993; Plumelle *et al.*, 1993; Pombo de Oliveira *et al.*, 1995). Furthermore, sporadic cases of ATLL have been described in Europe and the United States, mostly in immigrants

originating from regions of endemic HTLV-I infection (Rio *et al.*, 1990; Patey *et al.*, 1992; Matutes & Catovsky, 1994).

Figure 7. Estimated incidence rate of ATLL in persons (≥ 40 years) per 1 000 000 in Japanese prefectures during 1988–93



From the T- and B-cell Malignancy Study Group (1996)

Extensive reliable data concerning the occurrence of ATLL are available only for Japan and some Caribbean areas.

(ii) Age- and sex-distribution of ATLL

The average ages and sex ratios among ATLL cases are presented in Table 3. The average age of ATLL patients at diagnosis in Japan is 57 years (T- and B-cell Malignancy Study Group, 1988). The age pattern in Japan and the Caribbean is presented in Table 4 and Figure 8. No case of ATLL has been reported in children in Japan. In the Caribbean, South America and Africa, the mean age at ATLL onset is around 15 years younger, namely 40–45 years of age (Bartholomew *et al.*, 1985; Gibbs *et al.*, 1987; Gérard *et al.*, 1995; Pombo de Oliveira *et al.*, 1995). In addition, cases have been reported among children in Brazil (Pombo de Oliveira *et al.*, 1995). This suggests the presence of still unknown cofactors in the pathogenesis of this disease in areas of different environmental and cultural conditions or of a cohort effect on the proportion of HTLV-I carriers infected in early childhood (Manns, 1993).

In Japan, the estimated annual incidence of ATLL lies in the range 0.6–1.5 per 1000 HTLV-I carriers aged 40–59 years (Tajima & Kuroishi, 1985; Kondo *et al.*, 1989; Tokudome *et al.*, 1989). The rate appears to be similar in Jamaica (Murphy *et al.*, 1989b), but higher [6/1000] in the Noir-Marron population in French Guiana (Gérard *et al.*, 1995). The cumulative lifetime risk for ATLL among carriers has been estimated to lie in the range of 1–5% in both sexes in Japan and Jamaica (Kondo *et al.*, 1987, 1989;

Table 3. Average age, sex ratio and frequencies of abnormal clinical findings in patients with adult T-cell leukaemia/lymphoma

	Japan ^a (1984–85)	Japan ^b (1992–93)	Taiwan ^c (1983–90)	USA ^d (until Dec. 1991)	Jamaica ^e (1982–85)	Trinidad ^f and Tobago (1982–83)	French Guiana ^g (1990–93)	Brazil ^h [1989–93]	UK ⁱ [1982–94]
Number of cases	181	712	27	102	52	12	19	53 ^k	52
Average age (years)	56.9	58.9	48	~ 50	40	49.1	42.1	41	47
Age range (years)	24–90	25–87	28–71	7–75	20–70	22–84	21–71	2–65	19–77
Sex ratio (male versus female)	1.4	1.1	2.0	0.8	0.9	2.0	0.5	1.0	0.6
Skin lesions (%)	29.3	26.5	44	57	20	66.7	16	53	41
Hypercalcaemia (> 5.5 mEq/L) ^j (%)	17.1	23.6	37	72.5	48	58	53	34	51

Clinical findings on admission in Japanese cases in HTLV-I antibody positive cases

^aT- and B-cell Malignancy Study Group (1988); ^bT- and B-cell Malignancy Study Group (1996); ^cShih *et al.* (1992); ^dLevine *et al.* (1994); ^eGibbs *et al.* (1987); ^fBartholomew *et al.* (1985); ^gGérard *et al.* (1995); ^hPombo de Oliveira *et al.* (1995); ⁱMatutes & Catovsky (1994); ^jIn some of these series, calcium levels were measured on more than one occasion and this partially explains the variability of hypercalcaemia rates; ^kFive cases were HTLV-I negative by serology and PCR; there was 1 child and 52 adults.

Table 4. Estimated incidence of adult T-cell leukaemia/lymphoma per 1000 HTLV-I carriers per year in adult T-cell leukaemia/lymphoma endemic areas of Japan and Jamaica

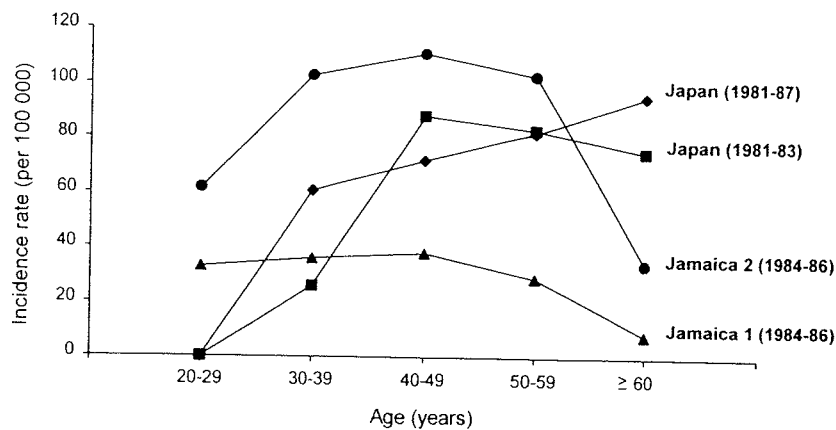
Age (years)	Japan (Uwajima): Kondo <i>et al.</i> (1989)			Japan (Saga): Tokudome <i>et al.</i> (1989)			Jamaica: Murphy <i>et al.</i> (1989b)			Jamaica: Murphy <i>et al.</i> (1989b) ^a		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
20-29	0	0	0	0	0	0	[0.31]	[0.34]	[0.33]	[0.45]	[0.76]	[0.62]
30-39	0.95	0.41	0.61	0.00	0.48	[0.26]	[0.47]	[0.31]	[0.36]	[0.94]	[1.10]	[1.03]
40-49	0.83	0.66	0.72	1.19	0.63	[0.88]	[0.64]	[0.28]	[0.38]	[1.12]	[1.10]	[1.11]
50-59	2.10	0.33	0.82	1.16	0.58	[0.83]	[0.61]	[0.18]	[0.29]	[1.26]	[0.83]	[1.03]
60	[1.45]	[0.68]	[0.95]	[0.96]	[0.63]	[0.75]	[0.11]	[0.07]	[0.08]	[0.31]	[0.38]	[0.34]
> 40	[1.50]	[0.58]	[0.89]	[1.06]	[0.61]	[0.93]	[0.34]	[0.15]	[0.21]	[0.80]	[0.71]	[0.75]
Cumulative rate												
(40-69)	[49.3]	[19.7]	[28.9]	[35.5]	[19.9]	[26.4]	[13.6]	[5.3]	[11.1]	[26.9]	[23.1]	[24.8]
(30-69)	[58.8]	[23.8]	[35.0]	[35.5]	[24.7]	[29.0]	[18.3]	[8.4]	[14.4]	[36.3]	[34.1]	[35.1]

^a Calculated from HTLV-I carriers defined as people who might have been infected with HTLV-I as a newborn baby.

[] Calculated by the Working Group

Murphy *et al.*, 1989b; Tokudome *et al.*, 1989) (Table 4). The age distributions of ATLL incidence for men and women in Kyushu, Japan, are shown in Figure 9.

Figure 8. Estimated annual age-specific incidence rates (per 100 000) of adult T-cell leukaemia/lymphoma among HTLV-I carriers in Japan and Jamaica



Sources: Japan, 1981–1987: Kondo *et al.* (1989); Japan, 1981–83: Tokudome *et al.* (1989); Jamaica: Murphy *et al.* (1989b)

Jamaica 2: calculated from HTLV-I carriers defined as people who might have been infected with HTLV-I as a newborn baby

(iii) Cohort studies

Tokudome *et al.* (1991) followed 3991 HTLV-I-seropositive blood donors aged ≥ 40 years from four blood centres in Kyushu who had donated blood between 1984 and 1987. Positivity for HTLV-I was determined by a particle agglutination antibody assay confirmed by indirect immunofluorescence in two centres. Mortality was ascertained through to August 1989; the average length of follow-up was 2.7 years for a total of 4403 person-years for men and 5591 person-years for women. The crude mortality rates for ATLL (3 deaths in men and 2 in women) were 68.1 per 100 000 for men and 35.8 for women. There were two additional deaths from malignant B-cell lymphoma (one in each sex).

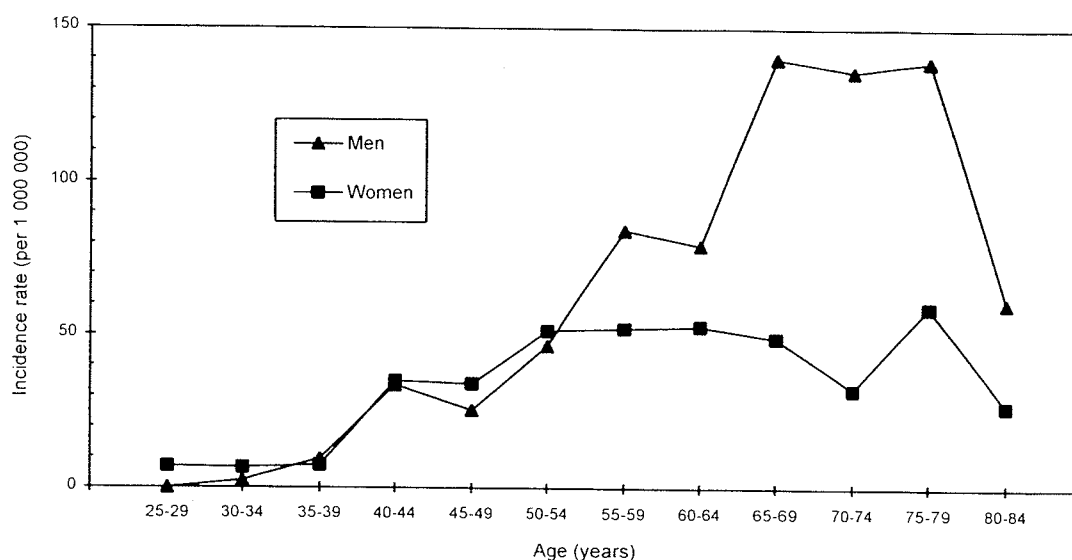
Iwata *et al.* (1994) followed a total of 1997 individuals aged ≥ 30 years from an HTLV-I-endemic community in Nagasaki Prefecture who were screened between 1984 and 1990. Of these, 503 (25.3%) were seropositive for HTLV-I by a particle agglutination antibody assay. The cohort was followed up to mid-1992, the average follow-up being 5.3 years for a total of 2581 person-years at risk. There were two deaths from ATLL (one in each sex). The crude mortality rate was 77 per 100 000 person-years. [No expected value was given but it must be very small.]

(iv) Case-control studies on co-factors

In ATLL-endemic areas, almost all ATLL cases diagnosed by clinicopathological features show seropositivity for HTLV-I (see Table 5). In areas of low ATLL incidence, a small proportion of cases lack HTLV-I antibody (T- and B-Cell Malignancy Group,

1985; Pombo de Oliveira, 1995), but the vast majority (> 90%) of cases are seropositive. The majority (> 60%) of all T-cell lymphomas in Jamaica and in Trinidad and Tobago are HTLV-I-seropositive versus less than 10% of other lymphoma cases (Manns *et al.*, 1993).

Figure 9. Estimated annual sex- and age-specific incidence rates (per 1 000 000) of adult T-cell leukaemia/lymphoma in Kyushu, Japan, 1992–93



From T- and B-cell Malignancy Study Group (1996)

Several case-control studies on ATLL have been conducted in Japan (T- and B-Cell Malignancy Study Group, 1985; Tokudome *et al.*, 1993). In one, 66 cases were compared with the same number of hospital controls without cancer selected by individual matching to each case for sex and age (within five years) (T- and B-Cell Malignancy Study Group, 1985). The investigators checked factors such as blood type (A, B, O), occupation, family history of cancer, habit of raising animals and habit of eating raw meat, but found no association of ATLL with any specific environmental risk factor. They found negative associations with hepatitis and blood transfusion. Tokudome *et al.* (1993) reported that the prevalence of smoking among 141 ATLL cases from northern Kyushu (Fukuoka and Saga) (65% of 75 men, 17% of 66 women) was significantly higher than that reported in the general population (53% and 4%, respectively). [The Working Group noted that smoking data from these cases may not be directly comparable to the general population rates, and that the inverse associations reported with hepatitis and transfusion history may be due to selection bias resulting from the use of hospitalized controls.]

To examine the importance of exposure to HTLV-I during early life (presumably from breast feeding), two groups have studied mothers of patients with ATLL and TSP/HAM. In both Jamaica (Wilks *et al.*, 1996) and Trinidad (Bartholomew *et al.*, 1994), 100% of mothers of ATLL patients were HTLV-I-infected compared with

Table 5. Proportion of anti-HTLV-I antibody-positive individuals in lymphoma cases and controls in Japan and Central/South America

	Japan (Kyushu) ^a	Japan (other districts) ^a	Brazil ^b	Jamaica ^d	Trinidad & Tobago ^d
	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)	Positive/tested (%)
T-cell lymphoma	162/192 (84.4)	60/142 (42.3)	50/188 (26.5)	41/70 (58.6)	34/43 (79.1)
ATLL	130/130 (100.0)	49/54 (90.7)	48/53 (90.5)	—	45/48 (94) ^c
Other T-cell lymphoma	32/62 (51.6)	11/88 (12.5)	1/29 (3.4)	—	—
Cutaneous T-cell lymphoma	—	—	0/54 (0)	—	—
Non-T-cell lymphoma	12/49 (24.5)	4/117 (3.4)	—	1/24 (4.2)	1/25 (4.0)
Healthy adults	241/3026 (8.0)	95/12 090 (0.8)	697/93 087 (0.7) ^c	27/376 (7.2)	20/355 (5.6)

^aT- and B-cell Malignancy Study Group (1985)^bPombo de Oliveira *et al.* (1995) except when noted^cMatutes *et al.* (1994)^dManns *et al.* (1993)^eCleghorn *et al.* (1990)

27–30% of mothers of TSP/HAM patients. The results indicate that infection early in life may be very important for the development of ATLL but that some cases of TSP/HAM occur following transmission of the virus later in life.

Studies of the role of the HLA system in relation to HTLV-I-associated disease are presented in Section 4.2.

2.1.2 *HTLV-I infection and cutaneous T-cell lymphomas*

Cutaneous T-cell lymphoma is an uncommon malignancy, with an estimated incidence of 800–1000 new cases per year in the United States (Weinstock *et al.*, 1988). It represents a small proportion (2–5%) of malignant lymphomas. A three-fold increase in the incidence of cutaneous T-cell lymphoma has occurred over the last couple of decades, although some of this increase may be due to improved diagnosis. The incidence of cutaneous T-cell lymphomas rises sharply with age and the average age of a patient at diagnosis is 52 years; the majority of new cases are over 30 years old. Men are affected more frequently than women. In the United States, cutaneous T-cell lymphoma has been found to be more prevalent in blacks than in whites (Pancake *et al.*, 1995).

When ATLL presents predominantly with cutaneous manifestations, it is sometimes indistinguishable from cutaneous T-cell lymphoma on clinical and pathological grounds (Arai *et al.*, 1994). Both are mature T-cell malignancies of CD4⁺, CD8[−] phenotype and affect the skin with a similar histological pattern of infiltration (Whittaker & Luzzatto, 1993; Whittaker *et al.*, 1993).

Over the past few years, a number of reports have indicated finding of HTLV-I and/or a related or partially deleted retrovirus in a subset of cutaneous T-cell lymphomas occurring in non-endemic areas (Hall *et al.*, 1991; Zucker-Franklin *et al.*, 1991; Srivastava *et al.*, 1992; Zucker-Franklin *et al.*, 1992; Pancake & Zucker-Franklin, 1993; Zucker-Franklin & Pancake, 1994; Manca *et al.*, 1994). However, HTLV-I-related sequences have not been found in other studies (Capésius *et al.*, 1991; Bazarbachi *et al.*, 1993, 1995; Matutes *et al.*, 1995b).

Even in the studies suggesting presence of the virus, the patients either lack antibodies to HTLV-I (Hall *et al.*, 1991; Zucker-Franklin *et al.*, 1991; Pancake & Zucker-Franklin, 1993) or show an indeterminate pattern of seroreactivity by the radioimmuno-precipitation assay (RIPA) and western blot, with weak p24 (Gag) reactivity but no anti-Tax or p19 (Gag) antibodies (Srivastava *et al.*, 1992). In one notable case, Picard *et al.* (1990) described one case first described as ATLL who was initially seronegative but produced antibodies several months after chemotherapy had begun; antibody studies were carried out with immunofluorescence techniques. In cases of cutaneous T-cell lymphoma positive for some part of HTLV-I (Gag, Pol or Env) by PCR, none contained a full-length proviral DNA; only one study has shown conservation of the pX region in cutaneous T-cell lymphoma, which is considered to be essential in the pathogenesis of ATLL (Manca *et al.*, 1994). Finally, with one possible exception (Hall *et al.*, 1994), no study has documented monoclonal or oligoclonal integration of HTLV-I in the neoplastic cells, another essential feature of HTLV-associated ATLL.

It is possible that, on occasion, endogenous retroviral sequences have been amplified accidentally using HTLV-I-specific PCR primers (Bangham *et al.*, 1988; Fujihara *et al.*, 1994). Another possibility is that some patients may have an incorrect diagnosis and are considered as having cutaneous T-cell lymphomas, when in fact they have a cutaneous form of ATLL with partial expression of the HTLV-I genome. It is therefore doubtful whether non-ATLL T-cell lymphomas are really associated with HTLV-I sequences.

2.1.3 HTLV-II infection

The role of HTLV-II in the pathogenesis of lymphoid neoplasms remains uncertain (Fouchard *et al.*, 1995). HTLV-II was first isolated from spleen cells of a patient with a T-cell malignancy diagnosed as a T-cell variant of hairy-cell leukaemia (Kalyanaraman *et al.*, 1982). In a subsequent case (Rosenblatt *et al.*, 1986), the patient was found to have two distinct neoplasms: a typical B-cell hairy-cell leukaemia in which HTLV-II was not detected and a CD8⁺ T-cell disorder equivalent to large granular-lymphocyte leukaemia in which HTLV-II was oligoclonally integrated (Rosenblatt *et al.*, 1988a,b). As the T-cell variant form of hairy-cell leukaemia is not a recognized entity among lymphoproliferative disorders, the original patient may have had a condition other than hairy-cell leukaemia.

In 1987, two groups reported finding that patients with large granular-lymphocyte leukaemia had a high prevalence (7/27 and 6/12, respectively) of antibodies against HTLV-II (Pandolfi *et al.*, 1987; Starkebaum *et al.*, 1987). The antibody profile seemed incomplete in most instances, prompting speculation that the response might be due to a related retrovirus. This leukaemia is a rare, chronic T-cell lymphoproliferation with a CD8⁺, CD4⁻ phenotype. The patients often present with splenomegaly and have an indolent course lasting for years.

Loughran *et al.* (1994) reported that six out of 28 patients with large granular-lymphocyte leukaemia were serologically positive for HTLV-I or HTLV-II by ELISA, although some had indeterminate patterns in which the western blot reacted only with either Gag protein or recombinant Env p21. Of these, only one patient with large granular-lymphocyte leukaemia was reported to have HTLV-II sequences in the lymphocytes, detected by PCR (using Pol and/or pX region primers) (Loughran *et al.*, 1992). However, in other cases reported, clonal integration of the retrovirus in the lymphoma cells was not found by Martin *et al.* (1993) and not investigated by Loughran *et al.* (1992, 1994), even though the patients had HTLV-II infection. Furthermore, Heneine *et al.* (1994) screened 51 patients with large granular-lymphocyte leukaemia but found only one to have HTLV-II antibodies. An unusual case of HTLV-I-positive ATLL with a blood picture similar to that of large granular-lymphocyte leukaemia has been reported in Japan (Sakamoto *et al.*, 1994).

Therefore, it remains doubtful whether HTLV-II plays a pathogenic role in large granular-lymphocyte leukaemia; undetected retroviruses or variant virus might be responsible (as proposed by Loughran *et al.*, 1994) or an indirect and non-specific mechanism may be involved (as proposed by Martin *et al.*, 1993).

One patient with mycosis fungoides associated with HTLV-II has been described (Zucker-Franklin *et al.*, 1992).

2.2 Other malignancies

2.2.1 HTLV-I

(a) Case reports and case series

One approach to studying the risk of other malignancies in HTLV-I-infected persons is to look at multiple cancers in ATLL patients. Most reports of such cases come from populations in Japan, where HTLV-I infection is endemic.

Ono *et al.* (1989) reported that, of 43 consecutive patients with ATLL seen in northern Kyushu (Saga) between 1982 and 1987, five (all aged ≥ 70 years) had additional multiple cancers, including two persons with triple separate malignancies. This was significantly higher than the two multiple cancers seen in 36 similarly aged cases with other haematological malignancies during the same time period (not adjusted for age or sex). The other second primary cancers seen in the cases of ATLL were tumours of the colon, larynx, thyroid, stomach (three), liver and kidney. Similarly, Imamura *et al.* (1993) found that five of 15 ATLL cases seen at one institution between 1963 and 1985 had a second malignancy (of the thyroid, stomach, larynx, lip and lung); this was significantly higher than the 44 multiple primaries among 1156 patients with other haematological malignancies (not adjusted for age or sex).

There have been various case reports of second non-T-cell primary malignancies in cases of ATLL, including two cases of Kaposi's sarcoma (Greenberg *et al.*, 1990; Veyssier-Belot *et al.*, 1990), an EBV-positive B-cell lymphoma (Tobinai *et al.*, 1991), an acute monoblastic leukaemia (Tokiooka *et al.*, 1992) and a cerebral small-cell lymphoma (Komori *et al.*, 1995). Shibata *et al.* (1995) described a Japanese HTLV-I carrier with a high prevalence (13%) of circulating abnormal lymphocytes and a long history of lymphadenopathy, having a tumour diagnosed as mantle-cell lymphoma with features of mucosa-associated lymphoid tissue lymphoma. EBV genome was not detectable in this B-cell tumour. In these case reports, no integrated HTLV-I provirus was found in the non-ATLL tumour. [The Working Group noted that in the reports of Ono *et al.* and Veyssier-Belot *et al.*, it is unclear whether the non-ATLL cases were tested for the presence of HTLV-I genome.]

A number of cases have been reported of HTLV-I detected by PCR in tumours other than ATLL. Since PCR will detect HTLV-I in infiltrating lymphocytes, the significance of such findings is open to question (Matsuzati *et al.*, 1990; Imajo *et al.*, 1993; Inoue *et al.*, 1994a).

Several reports dealing mainly with HTLV-I-endemic populations outside Japan describe chronic lymphocytic leukaemia in HTLV-I carriers. Blattner *et al.* (1983) reported that, of 14 cases of chronic lymphocytic leukaemia identified among a series of haematopoietic malignancies in Jamaica, four were HTLV-I-seropositive but were negative for HTLV-I provirus. Mann *et al.* (1987) reported experiments using tumour cells from two HTLV-I-seropositive Jamaicans with B-cell chronic lymphocytic

leukaemia. In these experiments, the cells were fused with a human B-lymphoblastoid cell line, and the secreted immunoglobulin was then characterized as to its antigen specificity for HTLV-I proteins. In one case, the antibodies reacted to the p24 Gag protein of HTLV-I, and in the other case, to the gp61 Env protein. The authors speculated that HTLV-I infection played an indirect role in the oncogenesis of antigen-committed B cells responding to the infection. [The Working Group noted that it was not clear whether the cases reported by Blattner *et al.* were of B-cell origin.]

Although there is a suggestion from case series of an excess of cancers other than ATLL among persons infected with HTLV-I, this is not supported by cohort studies (see below).

(b) Cohort studies

Tokudome *et al.* (1991) followed 3991 HTLV-I-seropositive blood donors aged ≥ 40 years from four communities in Kyushu who had donated blood between 1984 and 1987. Positivity for HTLV-I was determined by a particle agglutination antibody assay (see p. 297). Mortality was ascertained through to August 1989; the average length of follow-up was 2.7 years. Twenty-six deaths were reported in the cohort, four from malignancies (excluding those from ATLL and malignant lymphoma). Expected numbers were calculated on the basis of national age-specific rates. There was a significant deficit among HTLV-I carriers for deaths from other cancers: observed/expected, 0.32 (95% CI, 0.07–0.93) for men and 0.13 (95% CI, 0.00–0.71) for women. The authors noted that these findings are underestimates because of the healthy donor effect.

Iwata *et al.* (1994) followed up a total of 1997 individuals aged ≥ 30 years from an HTLV-I-endemic community in Nagasaki Prefecture for an average of 5.3 years (see p. 297). Population registries, death certificates and hospital records were used to identify a total of 120 deaths within the cohort; of these, 45 occurred among 503 HTLV-I carriers and included 10 non-ATLL malignancies. Based on proportionate mortality hazard, the risk for death from all other malignancies associated with HTLV-I infection was 1.2 (95% CI, 0.39–3.5) for men and 1.8 (0.61–5.2) for women.

(c) Case-control studies

In order to examine the association between HTLV-I infection and non-ATLL malignancies, Asou *et al.* (1986) identified 685 patients with malignancies other than ATLL (average age, 60 years) in 11 hospitals in central Kyushu (Kumamoto), Japan, between February and March 1985. Patients with an unknown history of blood transfusion were excluded. Seven patients had double malignancies. The comparison group included 22 726 healthy individuals who were part of a health survey by the Japanese Red Cross Health Service Center; all had lived in the Prefecture since early childhood. The two groups were compared for seroprevalence of HTLV-I as determined by ELISA, with adjustment for age and sex. The results were reported separately for cases according to whether or not they had a history of blood transfusion. The overall seroprevalence in the 394 non-transfused cases with other malignancies was 15.5% and for the 291 with a history of transfusion was 26.1%. The corresponding crude prevalence rate in the comparison population was 3.0%. The relative risk associated with HTLV-I

infection for malignancies other than ATLL was 2.2 ($p < 0.01$) among the non-transfused cases and 4.2 among the transfused cases ($p < 0.03$). [The Working Group noted that the controls were likely to be more healthy than the general population and were not stratified by transfusion history.]

A series of reports described an association of HTLV-I with hepatocellular carcinoma in Japan, which is commonly due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) (see IARC, 1994). Iida *et al.* (1988) evaluated the HTLV-I antibody status of 380 patients with various liver diseases including hepatocellular carcinoma in Kyushu (Kumamoto), Japan. HTLV-I seropositivity was determined by ELISA with western blot confirmation. For comparison, the overall seroprevalence rate in 62 000 blood donors from the area was 4.7%. The crude seroprevalence rate of 17.5% among the 40 cases of hepatocellular carcinoma was significantly higher than the comparison rates ($p < 0.001$); however, six of the seven seropositive cases had a history of transfusion. Among 93 cases of liver cirrhosis, a condition which almost always precedes the development of hepatocellular carcinoma, the HTLV-I seroprevalence of 10.8% was also significantly higher ($p < 0.01$), but 6 of the 10 seropositive cases had a history of transfusion. [The Working Group noted that it was unclear whether the higher HTLV-I infection rate in cases was due to disease-related transfusions or whether HTLV-I contributed to the occurrence of hepatocellular carcinoma. The data given are not sufficient to calculate age- and sex-adjusted estimates of relative risk.]

Kamihira *et al.* (1994) examined the prevalence of co-infection with HTLV-I and HCV and HBV in cases of liver disease including hepatocellular carcinoma in blood donors in Nagasaki. Cases included 181 cases of hepatocellular carcinoma seen at Nagasaki University Hospital and 228 cases of either chronic hepatitis or cirrhosis. Control data were obtained from 77 540 local blood donors. HTLV-I positivity was determined by particle agglutination assay and ELISA, with confirmation by western blot if necessary. [The Working Group noted that it was unclear whether positivity was based on either particle agglutination or ELISA or whether all sera were screened by both assays.] HBV status was detected by particle agglutination assays and HCV status by the first-generation ELISA. Among the control data, there was a significant association between HCV and HTLV-I infection (1.9% HCV-positive among 2907 HTLV-I seropositive versus 1.1% among 74 633 HTLV-I seronegative ($p = 0.04$)), but not between HBV and HTLV-I infections ($p = 0.70$). The mean age at hepatocellular carcinoma diagnosis among the 31 patients with HTLV-I antibody (61.5 years) was significantly lower than that of the 112 HTLV-I-seronegative cases (64.8 years; $p = 0.04$).

Okayama *et al.* (1995) examined the effect of HTLV-I co-infection on risk for HCV-positive hepatocellular carcinoma in comparison to HCV-positive chronic hepatitis. The cases included 43 sequentially seen hepatocellular carcinoma patients (33 men and 10 women) in southern Kyushu (Miyazaki), Japan, with a mean age of 62.4 years. The control group consisted of 127 biopsy-proven HCV-positive chronic hepatitis patients (86 men and 41 women) with a mean age of 51.7 years. All subjects were seropositive for HCV antibody and negative for HBV surface antigen. HTLV-I antibody status was determined by the particle agglutination assay, with confirmation by western blot. HCV

antibody status was determined by a second-generation ELISA. The HTLV-I seroprevalence among the cases of hepatocellular carcinoma was 30.2% and that among the chronic hepatitis controls was 9.5%. Among the 41 cases aged ≥ 50 years, 31.7% were HTLV-I carriers compared with 7.3% among the 82 HCV-positive chronic hepatitis patients of the same age ($p = 0.001$). With adjustment for broad age groups, the relative risk for HCV-positive hepatocellular carcinoma associated with co-infection with HTLV-I was 12.8 (95% CI, 3.3–52.3) among men; among women, there was no significant difference (relative risk, 1.3; 0.17–10.1). In this study, the prevalence of history of transfusion was similar among cases (42.9%) and chronic hepatitis controls (38.9%).

Several studies have examined the relationship between HTLV-I infection and human papillomavirus (HPV)-associated gynaecological malignancies (see IARC, 1995).

Miyazaki *et al.* (1991) examined the association of HTLV-I infection with gynaecological malignancies in patients from central Kyushu, Japan. Cases included 226 patients with gynaecological malignancies newly treated between April 1986 and July 1989, excluding those with a history of blood transfusion. The case group included 153 cervical cancer patients, 28 endometrial carcinoma patients, 37 ovarian carcinoma patients and 8 vaginal carcinoma patients. For comparison, the HTLV-I seroprevalence among 6701 healthy women seen at a mass health screening was used. HTLV-I status was determined by both immunofluorescence and ELISA assays. The relative risk for HTLV-I seroprevalence associated with cervical cancer among the 88 women aged ≤ 59 years was 2.9 ($p < 0.005$) and that for older cases was 1.7. Similarly, based on eight cases of vaginal carcinoma, the relative risk was 7.4 ($p < 0.001$). One of the latter cases also had smouldering ATLL. However, for the cases of endometrial and ovarian cancer, there was no association with HTLV-I (relative risks, 0.97 and 0.87, respectively). There was no significant association between HTLV-I status and stage of cervical cancer or the presence of regional node metastases in 59 patients who had primary radical surgery. However, HTLV-I status was predictive of recurrence among the cases of cervical and vaginal cancer combined ($p < 0.05$).

Strickler *et al.* (1995) evaluated the association between HTLV-I infection and the degree of cervical epithelial abnormalities. Cases for this case-control study were 49 out-patients with cervical intraepithelial neoplasia (CIN)-III or invasive carcinoma of the cervix sequentially seen at a colposcopy clinic in Jamaica between March 1992 and August 1993, from whom adequate tissue for analysis was available. Controls were 120 women diagnosed with benign, atypical squamous cells of unknown significance (ASCUS), CIN I or koilocytotic atypia. HTLV-I antibody status was determined by either a whole virus or recombinant gp21 ELISA with western blot confirmation. HPV DNA was detected by PCR, with typing for 11 sub-types (low, intermediate, high risk). As expected, there was a strong association with the detection of HPV DNA: 92.1% of cases were positive versus 25.7% in benign, 50% in ASCUS and 49.2% of the CIN I and koilocytotic atypia control subjects. HTLV-I seropositivity was greater among cases, who had more advanced stage (14.3%) than the controls (2.9%) (age-adjusted relative risk, 3.8; 95% CI, 1.03–14.2).

These case-control studies are summarized in Table 6. Overall, case-control studies of HTLV-I and risk of malignancies other than ATLL are few and may be influenced by selection bias (e.g., use of blood donors as controls). Significant positive associations were found for hepatocellular carcinoma and cancers of the female lower genital tract, which showed associations with HBV and HCV and with HPV, respectively. However, since these viruses are transmissible by similar routes to HTLV-I, the reported associations may be confounded.

2.2.2 *HTLV-II*

The majority of studies investigating an association between HTLV-I and malignancy have used assays which would also detect HTLV-II, and none has reported an association of HTLV-II with malignancy.